organ behave, and of their interaction with exogenous effectors and/or other model organs. Moreover, the device can contain many separate individual units, each having its own separate cell population and fluid environment, where each unit provides the same amount of shear stress or shear force on the living cells, and the device can include many such units, such as 96 units or 384 units or 1536 units, to conform to array sizes commonly used in high-throughput testing systems and protocols. Thus the device can be used for high-throughput testing in automated systems such as those conventionally used in various research programs and assay systems for testing of biochemical and biological model systems. This device is a significant advance toward creating model systems that accurately represent interactions among key components of the human body that advance pharmaceutical and medical research, and can help reduce the use of live animals in medical and pharmaceutical testing.

[0010] In one aspect, the invention provides a fluidic device comprising:

[0011] a manifold body comprising a substantially flat horizontal top surface, two or more separated flow channels, each of said flow channels having a horizontal section with a horizontal width, wherein each flow channel is connected to an inlet channel and an outlet channel, wherein the inlet channel and the outlet channel extend from the flow channel to the exterior of the manifold body;

[0012] the manifold body further comprising two or more holes extending downward from the top surface into the manifold body, wherein each of said holes intersects the horizontal section of one flow channel,

[0013] wherein each flow channel is configured so that fluid moving from the inlet channel through the horizontal section of the flow channel toward the outlet channel must pass through the portion of the flow channel that intersects at least one of the holes extending downward from the top surface of the manifold body. Note that naming of the inlet and outlet channels is somewhat arbitrary, as the roles of the two channels depend upon how the fluidic device is used. In some embodiments, the manifold body is constructed of two pieces. Optionally, the width of each hole where it intersects the flow channel is greater than the horizontal width of the flow channel at the point where the hole and flow channel intersect by a small amount. Optionally, additional layers can be added to the bottom of the manifold body.

[0014] In another aspect, the invention provides the fluidic device described above in combination with a multi-well cell culture plate adapted to be fitted to the fluidic device. The multi-well cell culture plate is adapted to provide a support or substrate suitable for growing living cells, either inside the wells of the cell culture plate or adhered to the bottoms of the wells where the cells can be exposed to liquid flowing in the flow channels of the fluidic device of the invention. In some embodiments, the cell culture plate is configured with 96 wells or more, such as 384 wells or 1536 wells. The multi-well cell culture plate can be selected from ones commercially available, and the fluidic device can be sized and configured to match such commercial cell culture plates.

[0015] In another aspect, the invention provides a system comprising the fluidic device described herein and a mechanism to cause fluid flow within the flow channels inside the manifold body of the fluidic device. In typical embodiments, the mechanism is capable of causing fluid to flow within the horizontal section of the flow channel of the fluidic device. In some of these systems, the mechanism to move fluid within the flow channel is selected from a pressure pump, a suction pump, flexible membrane disposed across an opening of the inlet channel or outlet channel of the fluidic device that can be deflected to move fluid, a bulb or balloon configured to apply suction or pressure to the fluid via the inlet channel or outlet channel of the fluidic device, and a mechanism to physically move the fluidic device in a reciprocating manner.

[0016] In another aspect the invention provides methods to use the fluidic devices and systems described herein to determine actions and/or reactions of living cells, especially living cells exposed to shear stress created by fluid flow in the flow channels of the fluidic devices of the invention. In some embodiments, the methods provide a model organ for various tests, either in isolation or in interactive combination with other model organs.

[0017] In another aspect, the invention provides a device to expose living cells to fluid shear stress, wherein the device comprises:

[0018] a plurality of wells having generally vertical walls and a generally horizontal floor, wherein at least a portion of the floor is a permeable membrane;

[0019] at least one flow channel positioned below the wells so that the permeable membrane portion of the floor of each well separates the well from one of the at least one flow channels; and

[0020] an inlet that connects the flow channel to the exterior of the device, and an outlet that connects the flow channel to the exterior of the device, wherein a fluid path leading from the inlet, through the flow channel to the outlet passes beneath the permeable membrane portion of the floor of at least one well.

[0021] Preferably, the plurality of wells are connected together by a generally horizontal plate in the form of a multi-well cell culture plate, and the multi-well cell culture plate can be separated from the remainder of the device.

[0022] The invention provides a method to use the device to expose living cells to fluid shear, which comprises placing cells on the permeable membrane of the device, and contacting the living cells with fluid moving within a flow channel of the device.

[0023] The following examples and detailed description highlight other aspects and embodiments of the invention. Other objects, advantages and features of the present invention will be apparent from the following specification taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIG. **1** is a side view of a cross-section of a testing unit of the fluidic device.

[0025] FIG. **2**A is a side view of a single testing unit of the device.

[0026] FIG. **2**B is a side view of a single testing unit with an added O-ring (**11***b*).

[0027] FIG. **3** depicts a top view of a 96-well cell culture plate for use with certain embodiments of the fluidic device.

[0028] FIG. **4**A and FIG. **4**B show the upper portion and lower portion, respectively, of a two-piece manifold body.